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22. A bone graft comprising at least one first cell having at least one first ~~exogenous~~ nucleic acid encoding at least one angiogenic protein and at least one ~~second~~ cell having at least one second nucleic acid encoding at least one ~~osteo~~genic protein, wherein the angiogenic protein is a vascular ~~endothelial~~ growth factor (VEGF), a connective tissue growth factor ~~(CTGF)~~, VEGF2, VEGF-C, an angiopoitein, an angiogenin, an angiogenin-2, or P1GF.

REMARKS

Summary of Invention

The invention is drawn to a method of enhancing bone density or formation (claims 1-18), a viral vector (claims 19-21), and a bone graft (claims 22-25).

Discussion of Office Action

The Office Action rejects claims 1-18 and 22-25 as including matter allegedly not described in the Specification, and it rejects all pending claims as allegedly not enabled. The Office Action further rejects claims 1-18 as indefinite. The Office Action also rejects claims 19-21 as obvious in light of Bonadio (U.S. Patent 5,942,496).

Discussion of Claim Amendments

Claims 1 and 22 are amended to clarify the identity of the recited angiogenic protein by removing reference to "angiopoetin homologous protein."

Claims 1 and 6 are amended to clarify the location of the first and second cells, respectively, as being within the bone or within a tissue immediately surrounding the bone. These amendments are supported in the specification, for example, on page 2, lines 18-20, and in the Example bridging pages 10 and 11.

These amendments add no new matter to the application. For the convenience of the Examiner, a marked-up illustration of the claims as amended is attached hereto, as is the text of all claims pending upon entry of this Amendment.

Discussion of Written Description Rejection

The Office Action rejects claims 1-18 and 22-25 under 35 U.S.C. § 112, first paragraph, as including matter allegedly not described in the Specification. In particular, the Office Action states that the application does not contain a written description of "angiopoetin homologous proteins." While applicants urge that such proteins would be known to those of ordinary skill in the art, to advance prosecution reference to "angiopoetin homologous protein" has been

removed from the claims. As amended, thus, the claims fully comply with Section 112, first paragraph. Accordingly, the rejection should be withdrawn.

Discussion of Enablement Rejection

The Office Action rejects claims 1-25 under 35 U.S.C. § 112, first paragraph, as non-enabled. Specifically, the Office Action urges that the term "region of the bone" is interpreted to mean anywhere in the body. As amended, the claims recite that the cell is "within the bone or within a tissue *immediately* surrounding the bone," not anywhere in the body. Accordingly, the claims, as amended, do not include the application of the nucleic acid "anywhere in the body."

The Office Action rejects the article previously cited as demonstrating viral targeting to bone (Matsubara et al., *Cancer Res., 61*, 6012-19 (2001)) on the basis that it was published after the filing date of the instant application. Applicants have previously noted that considerable progress has been made on viral targeting; Matsubara et al. certainly is not the only reference disclosing successful viral targeting. In fact, disclosure of such technology has been made part of the instant application by incorporating by reference the text of several patents that concern viral targeting (e.g., U.S. Patents 6,057,155, 5,962,311, 5,846,782, 5,770,442, 5,731,190, 5,712,136, and 5,559,099 (see page 6, lines 30-38; page 11, lines 22-28). As such, the specification in combination with the art as a whole fully enables the use of targeted viruses.

The previous Office Action asserted that the state of the art would not support an osteogenic role for the hedgehog proteins (Office Action, page 9, citing Lee et al.). However, it has been known for several years that hedgehog proteins are osteogenic proteins that can cause bone production in vivo. (see, e.g., Iwamoto et al., *Crit Rev Oral Biol Med., 10*(4), 477-86 (1999); Karp et al., *Development, 127*(3), 543-48 (2000); Kinto et al., *FEBS Lett., 404*(2-3), 319-23 (1997); Nakamura et al., *Biochem. Biophys. Res. Commun., 237*(2), 465-69 (1997) (attached)).

Because the specification, when read in combination with the art as a whole, enables the pending claims, the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Discussion of Indefiniteness Rejection

The Office Action rejects claims 1-25 under 35 U.S.C. § 112, second paragraph, as indefinite. In particular, the Office Action asserts that the term "cell associated with the region of the bone" is indefinite (Office Action, page 6). As noted above, as amended, the claims recite that the cell is "within the bone or within a tissue immediately surrounding the

bone." This is consistent with the statement in the specification concerning the "region of the bone" (see, e.g., specification page 2, lines 18-22, noting that the cell can be within this region prior to, during, or following the application of the inventive method). It is urged that those of skill in the art would understand the meaning of this language in the context of the present application. Accordingly, the rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Discussion of Obviousness Rejection - 35 U.S.C. § 103(a)

The Office Action rejects claims 19-23 as obvious in light of Bonadio for reasons of record. The previous Office Action urged that Bonadio discloses the transfer of a gene encoding FGF in combination with genes encoding other osteogenic proteins. However, this reference does not disclose or suggest a viral vector that has two transgenes – a "first nucleic acid" encoding an angiogenic protein and a "second nucleic acid" encoding an osteogenic protein. As such, Bonadio does not disclose the elements of claims 19-23, nor does it suggest the elements of those claims. Accordingly, Bonadio does not render claims 19-23 obvious, and the rejection under Section 103 should be withdrawn.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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In re Application of:

Crystal et al.

Application No. 09/629,074

Filed: July 31, 2000

For: METHOD OF ENHANCING BONE DENSITY

Art Unit: 1632

Examiner: Anne-Marie Baker

AMENDMENTS TO CLAIMS MADE IN RESPONSE TO OFFICE ACTION DATED NOVEMBER 23, 2001

1. (Twice Amended) A method for enhancing bone density or formation, the method comprising administering to at least one first cell associated with a region of a bone at least one first nucleic acid encoding at least one angiogenic protein, such that the first nucleic acid is expressed in the cell to produce the angiogenic protein, whereby bone density or formation is enhanced within the region; wherein the angiogenic protein is a vascular endothelial growth factor (VEGF), a connective tissue growth factor (CTGF), VEGF2, VEGF-C, an angiopoitein, [~~an angiopoetin homologous protein,~~] an angiogenin, an angiogenin-2, or P1GF, wherein the first cell is within the bone or within a tissue immediately surrounding the bone.

6. (Amended) The method of claim 1, further comprising administering to at least one second cell associated with the region at least one second nucleic acid encoding at least one osteogenic protein, such that the second nucleic acid is expressed in the cell to produce the osteogenic protein, wherein the second cell is within the bone or within a tissue immediately surrounding the bone.

22. (Twice Amended) A bone graft comprising at least one first cell having at least one first exogenous nucleic acid encoding at least one angiogenic protein and at least one second cell having at least one second nucleic acid encoding at least one osteogenic protein, wherein the angiogenic protein is a vascular endothelial growth factor (VEGF), a connective tissue growth factor (CTGF), VEGF2, VEGF-C, an angiopoitein, [~~an angiopoetin homologous protein,~~] an angiogenin, an angiogenin-2, or P1GF.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Crystal et al.

Application No. 09/629,074

Art Unit: 1632

Examiner: Anne-Marie Baker

Filed: July 31, 2000

For: METHOD OF ENHANCING BONE DENSITY

CLAIMS PENDING UPON ENTRY OF THE AMENDMENTS MADE IN RESPONSE TO OFFICE ACTION DATED NOVEMBER 23, 2001

1. A method for enhancing bone density or formation, the method comprising administering to at least one first cell associated with a region of a bone at least one first nucleic acid encoding at least one angiogenic protein, such that the first nucleic acid is expressed in the cell to produce the angiogenic protein, whereby bone density or formation is enhanced within the region; wherein the angiogenic protein is a vascular endothelial growth factor (VEGF), a connective tissue growth factor (CTGF), VEGF2, VEGF-C, an angiopoitein, an angiogenin, an angiogenin-2, or P1GF, wherein the first cell is within the bone or within a tissue immediately surrounding the bone.

2. The method of claim 1, wherein at least one of the nucleic acids is exposed to at least one cell in vivo in the region of the bone.

3. The method of claim 1, wherein at least one of the nucleic acids is exposed to at least one cell ex vivo, which is then delivered in vivo to the region of the bone.

4. The method of claim 1, wherein the angiogenic protein is $VEGF_{121}$ or $VEGF_{165}$.

5. The method of claim 1, wherein the angiogenic protein is selected from the group consisting of $VEGF_{121}$, $VEGFA_{138}$, $VEGFA_{162}$, $VEGF_{165}$, $VEGF_{182}$, and $VEGF_{189}$.

6. The method of claim 1, further comprising administering to at least one second cell associated with the region at least one second nucleic acid encoding at least one osteogenic protein, such that the second nucleic acid is expressed in the cell to produce the osteogenic protein, wherein the second cell is within the bone or within a tissue immediately surrounding the bone.

7. The method of claim 6, wherein the osteogenic protein is selected from the group consisting of a bone morphogenic protein (BMP), a transforming growth factor (TGF), a latent TGF binding protein (LTBP), latent membrane protein-1 (LMP-1), a heparin-binding

neurotrophic factor (HBNF), growth and differentiation factor-5 (GDF-5), a parathyroid hormone (PTH), a fibroblast growth factor (FGF), an epidermal growth factor (EGF), a platelet-derived growth factor (PDGF), an insulin-like growth factor, a growth factor receptor, a cytokine, a chemotactic factor, a LIM mineralization protein (LMP), a leukemia inhibitory factor (LIF), a hedgehog protein, and midkine (MK).

8. The method of claim 6, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7 and BMP-8.

9. The method of claim 6, wherein the osteogenic protein is TGF-b1.

10. The method of claim 6, wherein the osteogenic protein is BMP-2.

11. The method of claim 6, wherein the osteogenic protein is MK.

12. The method of claim 6, wherein the osteogenic protein is HBNF.

13. The method of claim 6, wherein the angiogenic protein is a VEGF, and the osteogenic protein is TGF-b1.

14. The method of claim 6, wherein the angiogenic protein is a VEGF, and the osteogenic protein is BMP-2.

15. The method of claim 6, wherein the angiogenic protein is a VEGF, and the osteogenic protein is MK.

16. The method of claim 6, wherein the angiogenic protein is a VEGF, and the osteogenic protein is HBNF.

17. The method of claim 6, wherein the first cell and the second cell are the same cell.

18. The method of claim 6, wherein the first nucleic acid and the second nucleic acid are the same nucleic acid.

19. A viral vector comprising at least one first nucleic acid encoding at least one angiogenic protein and at least one second nucleic acid encoding at least one osteogenic protein.

20. The viral vector of claim 19, which is an adenoviral vector.

21. The viral vector 19, which is deficient in at least one essential gene function.

22. A bone graft comprising at least one first cell having at least one first exogenous nucleic acid encoding at least one angiogenic protein and at least one second cell having at least one second nucleic acid encoding at least one osteogenic protein, wherein the angiogenic protein is a vascular endothelial growth factor (VEGF), a connective tissue growth factor (CTGF), VEGF2, VEGF-C, an angiopoitein, an angiogenin, an angiogenin-2, or P1GF.

23. The bone graft of claim 22, wherein the osteogenic protein is selected from the group consisting of a bone morphogenic protein (BMP), a transforming growth factor (TGF),

a latent TGF binding protein (LTBP), latent membrane protein-1 (LMP-1), a heparin-binding neurotrophic factor (HBNF), growth and differentiation factor-5 (GDF-5), a parathyroid hormone (PTH), a fibroblast growth factor (FGF), an epidermal growth factor (EGF), a platelet-derived growth factor (PDGF), an insulin-like growth factor (IGF), a growth factor receptor, a cytokine, a chemotactic factor, a LIM mineralization protein (LMP), a leukemia inhibitory factor (LIF), a hedgehog protein, and midkine (MK).

24. The bone graft of claim 22, wherein the angiogenic protein is a vascular endothelial growth factor (VEGF).

25. The bone graft of claim 22, which is an allograft.